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(54) Benzimidazole derivatives, their production and use

Benzimidazolderivate, Verfahren zu deren Herstellung und Anwendung

Dérivés de benzimidazole, leur préparation et utilisation

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(56) References cited:
EP-A- 0 392 317
EP-A- 0 399 732
EP-A- 0 400 835
EP-A- 0 420 237

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Description

FIELD OF THE INVENTION

The present invention relates to novel benzimidazole derivatives having potent pharmacological actions and intermediates for the preparation thereof. More particularly, the present invention relates to compounds having potent anti-hypertensive activity and strong angiotensin II antagonistic activity, which are useful as therapeutic agents for treating circulatory diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, nephritis, etc.

BACKGROUND OF THE INVENTION

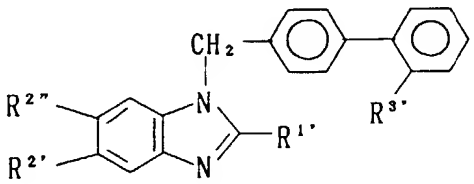
The renin-angiotensin system is involved in the homeostatic function to control systemic blood pressure, the volume of body fluid, balance among the electrolytes, etc., associated with the aldosterone system. Development of angiotensin II converting enzyme inhibitors (ACE inhibitor) (this converting enzyme produces angiotensin II which possesses a strong vasoconstrictive action) has clarified the relation between the renin-angiotensin system and hypertension. Since angiotensin II constricts blood vessel to elevate blood pressure via the angiotensin II receptors on the cellular membranes, angiotensin II antagonists, like the ACE inhibitor, would be useful in treating hypertension caused by angiotensin.

It has been reported that various angiotensin II analogues such as saralasin, [Sar^1,Ile^8]A II, and the like, possess potent angiotensin II antagonist activity.

It has, however, been reported that, when peptide antagonists are administered parenterally, their actions are not prolonged and, when administered orally, they are ineffective (M. A. Ondetti and D. W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

It would be highly desirable to develop a non-peptide angiotensin II antagonist which overcomes these drawbacks. In the earliest studies in this field, imidazole derivatives having angiotensin II antagonist activity have been disclosed in Japanese Patent Laid Open No. 71073/1981; No. 71074/1981; No. 92270/1982; No. 157768/1983; USP No. 4,355,040, No. 4,340,598, etc. Later, improved imidazole derivatives are disclosed in European Patent Laid Open No. 0253310, No. 0291969, No. 0324377, Japanese Patent Laid Open No. 23868/1988; and No. 117876/1989. Further, pyrole, pyrazole, and triazole derivatives are disclosed as angiotensin II antagonists in European Patent Laid Open No. 0323841, and Japanese Patent Laid Open No. 287071/1989.

USP No. 4,880,804 discloses benzimidazole derivatives having an angiotensin II receptor antagonistic action, which are intravenously active in vivo in rats with renal hypertension. Examples of such benzimidazole derivatives are those represented by the following formula (A):



(A)

wherein substituents, for example, in the 5- and/or 6-position are hydroxymethyl, methoxy, formyl, chloro, or carboxy. Although most compounds among those exemplified are orally inactive, it is said that only the 6-hydroxymethyl and 6-chloro compounds are orally effective (100 mg/kg or less). It is, however, believed that the activity of even these disclosed compounds is insufficient for clinical uses.

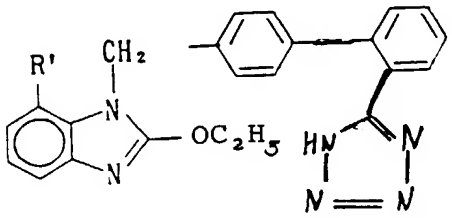
SUMMARY OF THE INVENTION

The present invention provides novel benzimidazole derivatives having potent anti-hypertensive activity and strong angiotensin II antagonistic action, which are of practical value in clinical use as therapeutic agents.

The present inventors considered that compounds functioning to control the renin-angiotensin system as well as clinically useful for the treatment of circulatory diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, etc. are required to have potent angiotensin II receptor antagonistic activity and to exert strong oral and long-lasting angiotensin II antagonist action. Extensive investigations were made based on those consideration. As a result of this research, the present inventors have suc-

ceeded in synthesizing novel 2-substituted benzimidazole derivatives (I) possessing highly angiotensin II receptor antagonistic activity as well as exerting strong oral and long-lasting angiotensin II antagonistic and anti-hypertensive action and developed the present invention.

The present invention relates to benzimidazole derivatives having the formula I:



(I)

wherein R' is carboxyl or 1-(cyclohexyloxycarbonyloxy)-ethoxycarbonyl and the pharmaceutically acceptable salts thereof.

These compounds are unexpectedly potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, nephritis, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the benzimidazole derivative having the formula I and a pharmaceutically acceptable carrier useful in treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, renal failure, nephritis, etc., and processes for preparing such compounds and compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a X ray scattering chart obtained in Experimental Example 1.

FIG. 2 depicts an IR spectrum pattern obtained in Experimental Example 1.

FIG. 3 depicts a differential scanning calorimeter pattern obtained in Experimental Example 1.

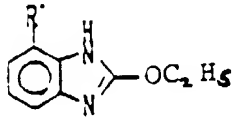
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the benzimidazole derivatives (I) and the pharmaceutically acceptable salts thereof, which possess strong angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive diseases, heart diseases, strokes, cerebral diseases, nephritis, etc., pharmaceutical compositions comprising an effective amount of the benzimidazole derivative having the formula I and a pharmaceutically acceptable carrier useful in treating said circulatory diseases, and processes for preparing such compounds and compositions.

The compounds of the present invention are 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylic acid or a pharmaceutically acceptable salt thereof and 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

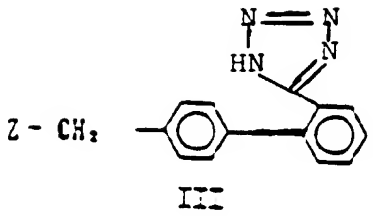
EP-A1-400 835, EP-A1-420 237, EP-A1-399 732 and EP-A1-392 317, which all are earlier patent documents but published after the priority date of the present case, relate to benzimidazoles with different substituents.

The compounds of the present invention may be prepared by (i) reacting a compound of the formula (II):



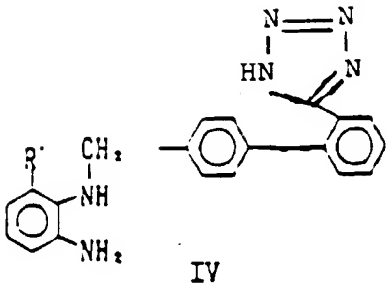
II

wherein R' has the above-defined meaning, or a salt thereof, with a compound of the formula (III):



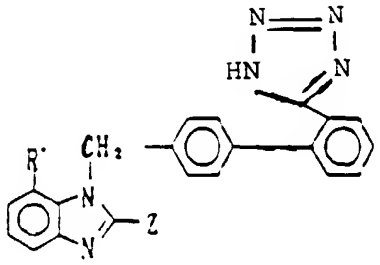
III

wherein Z is halogen, (ii) reacting a compound of the formula (IV):



IV

wherein R' has the above-defined meaning, or a salt thereof, with an alkyl orthocarbonate or a carbonylating reagent or (iii) reacting a compound of the formula (V'):



wherein each group has the above-defined meaning or a salt thereof, with a nucleophilic reagent, and, if desired, converting a product obtained by the above processes (i) to (iii) into a compound of the formula (I) by nucleophilic reaction, acylation, esterification, and/or deprotection, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

The first reaction step is an alkylation using an alkylating agent in the presence of a base. One molar portion of the compound (II) is employed with approximately 1 to 3 moles of the base and 1 - 3 moles of the alkylating agent. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, tetrahydrofuran, acetone, ethylmethylketone, and the like. Examples of such bases include sodium hydride, potassium t-butoxide, potassium carbonate and sodium carbonate. Examples of such alkylating agents include chlorides, bromides, iodides. The reaction conditions may vary depending on the combination of the base and the alkylating agent. Advantageously, the reaction is carried out at ice-cooling to room temperature for 1 - 10 hours.

In the said alkylation, a mixture of two isomers is usually obtained. These two compounds can be obtained easily as pure products respectively by conventional isolation and/or purification methods (e.g. recrystallization or column chromatography).

The reaction of a phenylenediamine (IV) with alkyl orthocarbonate is conducted in the presence of an acid by using alkyl orthocarbonate of 1 to 3 mol. relative to Compound (IV). By using ,for example, acetic acid or p-toluenesulfonic acid, the reaction is accelerated to afford a ring-closed compound in a good yield. As the reaction solvent, halogenated hydrocarbons and ethers can be employed but, usually, it is more convenient to conduct the reaction without a solvent. The reaction is usually conducted at 70 to 100°C for 1 to 5 hours. In this reaction, a dialkoxyimino compound is produced as the reaction intermediate, which is then ring-closed into the 2-alkoxy compound in the presence of the acid in the

reaction system. It is also possible to isolate the reaction intermediate, which is then subjected to ring-closure reaction in the presence of an acid to form the 2-alkoxy compound.

The phenylenediamino compound (IV) may be reacted with various reagents to give the 2-keto compound (or the 2-hydroxy compound) by using a carbonylating reagent (e.g. urea, diethyl carbonate, bis(1-imidazolyl)ketone, etc.) in an amount of 1 to 5 mol. relative to 1 mol. of Compound (IV) and, usually, by using, among others, halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.), alcohols (e.g. methanol, ethanol, etc.) or amides (e.g. dimethylformamide, dimethylacetamide, etc.).

The 2-hydroxy compound is selectively 0-alkylated with a Meerwein reagent to give the 2-alkoxy compound. This reaction is conducted by using the Meerwein reagent in an amount of 1 to 3 mol., usually, employing, as the solvent, halogenated hydrocarbons (e.g. methylene chloride, chloroform, etc.) or ethers (e.g. methyl ether, ethyl ether, etc.). Examples of such Meerwein reagents include, among others, trimethyl oxonium fluoroborate ($Me_3O^+BF_4^-$), triethyl oxonium fluoroborate ($Et_3O^+BF_4^-$), etc. These are preferably used by in situ preparation according to the method described in literature references [H. Meerwein, Org. Syn. 46. 113 and 120(1966)]. The reaction is preferably conducted at temperatures ranging from room temperatures to the boiling point of the solvent used for 2 to 20 hours.

A 2-halogeno compound (V') may be reacted with various nucleophilic reagents to form the compound (I). The reaction can be carried out according to the procedures as described in known references (e.g. D. Harrison and J. J. Ralph, J. Chem. Soc., 1965, 236). A 2-hydroxy compound is reacted with a halogenating reagent (e.g. phosphorus oxychloride, phosphorus trichloride, etc.) to form the 2-halogeno compound (V') which is reacted with various nucleophilic reagents (e.g. alcohols, mercaptans, amines, etc.) in a suitable organic solvent to give the compound (I). The reaction conditions may vary depending on the nucleophilic reagent employed. Upon the reaction with alcohols, alcoholates (e.g. sodium methoxide, sodium ethoxide, sodium propoxide, etc.) derived from alcohols and sodium metal are preferably used. As the reaction solvent, alcohols then used for nucleophilic reagents can be employed. Relative to 1 mol. of the compound (V'), there is used 2 to 5 mol. of an alcoholate. Advantageously, the reaction is usually conducted at the boiling point of the solvent used for 1 to 3 hours. Upon the reaction with amines, 3 to 10 mol. of an amine is used relative to 1 mol. of the compound (V'). As the reaction solvent, alcohols (e.g. ethanol, etc.) are employed but, an excess amount of amines can be used. Advantageously, the reaction is usually conducted at temperatures ranging from the boiling point of the solvent to 150°C for 1 to 10 hours. Upon the reaction with mercaptans, 2 to 5 mol. of a mercaptan is used relative to 1 mol. of the compound (V'). The reaction is preferably conducted in the presence of 1 to 3 mol. of an base (e.g. sodium carbonate, potassium carbonate, etc.) relative to Compound (IV). Examples of solvents include acetonitrile, alcohols, halogenated hydrocarbons (e.g. chloroform, dichloroethane, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.) or amides (e.g. dimethylformamide, dimethylacetamide, etc.). The reaction can be conducted preferably at temperatures ranging from 50°C to the boiling point of the solvent for 1 to 5 hours.

A protected tetrazole derivative is deprotected. Conditions of the deprotection depend on the protective group (R) then used. When R is triphenylmethyl, 2-tetrahydropyranyl, methoxymethyl, or ethoxy methyl, it is convenient to conduct the reaction in an aqueous alcohol (e.g. methanol, ethanol, etc.) containing 0.5N to 2N hydrochloric acid or acetic acid at room temperatures for 1 to 10 hours.

The reaction products obtained as above, can be easily isolated and/or purified by or according to conventional methods such as, for example, evaporation of solvents, extraction by water or organic solvents, concentration, neutralization, recrystallization, distillation or column chromatography. The compounds (I) thus produced can be isolated and/or purified from the reaction mixture according to conventional methods such as, for example, recrystallization and column chromatography, to obtain a crystalline product.

The compounds obtained as above, may be in the form of solvates or salts (including addition salts) derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, citric acid, ascorbic acid, lactic acid, p-toluenesulfonic acid, methanesulfonic acid, fumaric acid, tartaric acid and maleic acid. Other salts include salts with ammonium, alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases (e.g. trialkylamines, dibenzylamine, ethanolamine, triethanolamine, N-methylmorpholine, etc).

And, by conventional means, the compounds (I) can be formed as salts with non-toxic, physiologically or pharmaceutically acceptable acids or bases, for example salts with an inorganic acid such as hydrochloride, sulfate or nitrate, and, depending on compounds, salts with an organic acid such as acetate, oxalate, succinate or maleate, salts with an alkali metal such as sodium salt or potassium salt, or salts with an alkaline earth metal such as calcium salt.

For the synthesis of these compounds (I), the starting compounds (II) and (IV) can be synthesized by or according to the methods described in, for example, the following literature references or methods analogous thereto, namely, by the reactions (M), (N), (0) and (P) as depicted below.

(1) P. N. Preston, The Chemistry of Heterocyclic Compounds, Vol. 40, ed. by P. N. Preston, John Wiley & Sons Inc., New York (1981), pp. 1-286,

(2) E. S. Schipper and A. R. Day, Heterocyclic Compounds, Vol. 5, ed. by R. C. Elderfield, John Wiley & Sons Inc., New York (1965), pp. 194-297,
(3) N. J. Leonard, D. Y. Curtin, & K. M. Beck, J. Am. Chem. Soc. 69, 2459 (1947),
(4) S. Weiss, H. Michaud, H. Prietzel, & H. Kromer, Angew. Chem. 85, 866 (1973),
(5) W. B. Wright, J. Heterocycl. Chem., 2, 41 (1965),
(6) A. M. E. Omar, Synthesis, 1974, 41,
(7) D. J. Brown & R. K. Lynn, J. Chem. Soc.(Perkin I), 1974, 349,
(8) J. A. Van Allan & B. D. Deacon, Org. Syn., 30, 56 (1950),
(9) S. P. Singh, S. S. Parmar & B. R. Pandey, J. Heterocycl. Chem., 14, 1093 (1977),
(10) S. Nakajima, I. Tanaka, T. Seki & T. Anmo, Yakugaku Zasshi, 78, 1378 (1959),
(11) K. Seno, S. Hagishita, T. Sato & K. Kuriyama, J. Chem. Soc., Perkin Trans. 1984, 2013,
(12) D. R. Buckle et al., J. Med. Chem., 30, 2216 (1987),
(13) R. P. Gupta, C. A. Larroquette & K. C. Agrawal, J. Med. Chem., 25, 1342 (1982), etc.

The compounds and the salts thereof according to the invention are less toxic, strongly inhibit the vasoconstrictive and hypertensive actions of angiotensin II, exert a hypotensive effect in animals, in particular mammals (e.g. human, dog, rabbit, rat, etc.), and therefore they are useful as therapeutics for not only hypertension but also circulatory diseases such as heart failure (hypertrophy of the heart, cardiac insufficiency or cardiac infarction), strokes, cerebral apoplexy, nephropathy and nephritis. The compounds (I) and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, pigs, rabbits, rats, etc.). Further, the compounds (I) and salts thereof according to the present invention are of quite low toxicity and clinically useful in treating not only hypertension but also circulatory system diseases such as heart and brain diseases, strokes, renal failures and nephritis.

For therapeutic use, the compounds (I) and salts thereof can be orally, parenterally, by inhalation spray, rectally, or topically administered as pharmaceutical compositions or formulations (e.g. powders, granules, tablets, pills, capsules, injections, syrups, emulsions, elixirs, suspensions, solutions) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intraperitoneal injections, or infusion techniques. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in water. Among the acceptable vehicles or solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil or fatty acid may be employed including natural, synthetic, or semisynthetic fatty oils or acids, and natural, synthetic, or semisynthetic mono-, di-, or triglycerides.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug. Solid dosage forms for oral administration may include powders, granules, tablets, pills, and capsules as mentioned above. In such solid dosage forms, the active compound may be admixed with at least one additive such as sucrose, lactose, celluloses, mannitol, maltitol, dextran, starches, agars, alginates, chitins, chitosans, pectins, tragacanth gums, arabic gums, gelatins, collagens, casein, albumin, and synthetic or semisynthetic polymers or glycerides. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents as magnesium stearate, preservatives such as parabens and sorbic acid, antioxidants such as ascorbic acid, α-tocopherol and cysteine, disintegrants, binders, thickening, buffering, sweetening, flavoring, and perfuming agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, solutions containing inert diluents commonly used in the art, such as water.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The dose varies with the diseases to be treated, symptoms, subjects and administration routes, and it is desirable that a daily dose of 1 to 50 mg for oral administration or 1 to 30 mg for intravenous injection is divided into 2 to 3 administrations when used as an agent for the therapy in adults. For example, when used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, 10 mg to 100 mg a day orally and 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds.

Examples

By the following formulation examples, working examples, experimental examples and reference examples, the present invention will be explained more concretely, but they should not be interpreted as limiting the invention in any manner.

Examples of abbreviations in this specification are as follows:

Me: methyl, Et: ethyl, Tet: tetrazolyl, cycl: cyclo-, Pr: propyl, Bu: butyl, Pen: pentyl, Bu: butyl, Hex: hexyl, Hep: heptyl, Ph: phenyl, DMF: dimethylformamide, and THF: tetrahydrofuran.

Formulation Examples

When the compound (I) of the present invention is used as a therapeutic agent for circulatory failures such as hypertension, heart diseases, strokes, kidney diseases, etc., it can be used in accordance with, for example, the following formulations.

1. Capsules

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid	10 mg
(2)	lactose	90 mg
(3)	fine crystalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

2. Tablets

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
	one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

3. Capsules

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate	10 mg
(2)	lactose	90 mg
(3)	fine crystalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

4. Tablets

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
	one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

5. Injections

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid disodium salt	10 mg
(2)	inositol	100 mg
(3)	benzyl alcohol	20 mg
	one ampoule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.

Reference Example 1

Ethyl 2-carboxy-3-nitrobenzoate

A mixture of 3-nitrophthalic acid (35 g) in ethanol (300 ml) containing conc. sulfuric acid (20 ml) was heated under reflux for 24 hours. The solvent was evaporated in vacuo and the residue was poured into cold water (700 ml). The mixture was extracted with ethyl acetate. The organic layer was washed with water and shaken with an aqueous solution of potassium carbonate. The aqueous layer was made acidic with hydrochloric acid and the mixture was extracted with methylene chloride. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The resultant solid (29 g, 74%) was used for the subsequent reaction without purification.
^{1}H-NMR(90MHz, $CDCl_3$) δ: 1.43(3H,t), 4.47(2H,q), 7.70(1H,t), 8.40(2H,d), 9.87(1H,br s)
IR(Nujol) cm^{-1}: 1725, 1535, 1350, 1300, 1270

Reference Example 2

Ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate

A mixture of ethyl 2-carboxy-3-nitrobenzoate (23.9 g) and thionyl chloride (12 ml) in benzene (150 ml) were heated under reflux for 3 hours. The reaction mixture was concentrated to dryness. The resultant acid chloride (26 g, quantitative) was dissolved in methylene chloride (20 ml). The solution was added dropwise to a mixture of sodium azide (9.75 g) in dimethylformamide(DMF) (20 ml) with stirring vigorously. The reaction mixture was poured into a mixture of ether-hexane (3 : 1, 200 ml) and water (250 ml) to separate into two layers. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The residue was dissolved in t-butanol (200 ml) and the solution was heated gradually with stirring, followed by heating under reflux for 2 hours. The reaction mixture was concentrated in vacuo to give an oily product (30 g).
^{1}H-NMR(90MHz, $CDCl_3$) δ : 1.40(3H,t), 1.53(9H,s), 4.43(2H,q), 7.23(1H,t), 8.03-8.27(2H,m), 9.70(1H,br s)
IR(Neat) cm^{-1}: 3320, 2980, 1740, 1585, 1535, 1500, 1440, 1375, 1265, 1155

Working Example 1

Ethyl 2-[[2'-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate

To a solution of ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate (20 g) in tetrahydrofuran (50 ml) was added, while stirring under ice-cooling, sodium hydride (60% dispersion in mineral oil, 2.8 g). The mixture was stirred at room temperature for 20 minutes and to the mixture were then added 4-(2-cyanophenyl)benzyl bromide (18 g) and potassium iodide (360 mg), followed by heating for 10 hours under reflux. The solvent was evaporated to dryness and the residue was partitioned between water (250 ml) and ether (200 ml). The organic layer was washed with water, dried and concentrated to give a yellow syrup. The syrup was dissolved in a mixture of trifluoroacetic acid (60 ml) and methylene chloride (40 ml) and the solution was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and to the residue was added ethyl ether (200 ml) to give crystals. The crystals were collected by filtration, washed with ether to give pale yellow crystals (22.1 g, 85%), m.p. 118-119°C.

^{1}H-NMR(90MHz,$CDCl_3$) δ : 1.37(3H,t), 4.23(2H,s), 4.37(2H,q), 6.37(1H,t), 7.33-7.83(9H,m), 7.97-8.20(2H,m)

IR(Nujol)cm-1: 3280, 2220, 1690, 1575, 1530, 1480, 1450, 1255, 1105, 755

Working Example 2

Ethyl 3-amino-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate

To a solution of ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]nitrobenzoate (10.4 g) in ethanol (50 ml) was added stannous dichloride dihydrate (28.1 g) and the mixture was stirred at 80°C for two hours. The solvent was evaporated to dryness. To the ice-cooling mixture of the residue in ethyl acetate (300 ml) was added dropwise 2N NaOH (500 ml) with stirring. The aqueous layer was extracted with ethyl acetate (200 ml x 2). The organic layers were combined, washed with water, and dried. The solvent was evaporated to dryness and the residue was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - hexane gave colorless crystals (7.3 g, 79%), m.p. 104-105°C.

^{1}H-NMR(200MHz, $CDCl_3$) δ: 1.33(3H,t), 4.23(2H,s), 4.27(2H,q), 6.83-6.93(2H,m), 7.35-7.55(7H,m), 7.64(1H,dt), 7.76 (dd)

IR(KBr) cm^{-1}: 3445, 3350, 2220, 1680, 1470, 1280, 1240, 1185, 1160, 1070, 1050, 1020, 805, 750

Working Example 3

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

Acetic acid (0.2 g) was added to a solution of ethyl 3-amino-2-N-[2'-cyanobiphenyl-4-yl)methyl]aminobenzoate (1.0 g) in ethyl orthocarbonate (5 ml). The mixture was stirred at 80°C for one hour. The reaction mixture was concentrated, and the concentrate was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water. The solvent was evaporated to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.79 g, 69%), m.p. 131-132°C.

Elemental Analysis for $C_{26}H_{23}N_3O_3$:			
	C(%)	H(%)	N(%)
Calcd.:	73.39;	5.45;	9.88
Found :	73.36;	5.42	9.83

^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.24(3H,t), 1.49(3H,t), 4.24(2H,q), 4.68(2H,q), 5.72(2H,s), 7.10(2H,d), 7.19(1H,t), 7.38-7.46(4H,m), 7.56-7.66(2H,m), 7.73-7.77(2H,m)

IR(KBr) cm^{-1}: 2220, 1720, 1550, 1480, 1430, 1280, 1245, 1215, 1040, 760. 740

Working Example 4

Ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

To a solution of ethyl 2-chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]benzimidazole-7-carboxylate (1.0 g) in ethanol (30 ml) was added NaOEt (0.17 g) and the mixture was heated under reflux for 1 hour. The reaction mixture was concen-

trated to dryness. The resultant residue was dissolved in ethyl acetate and the solution was washed with water, and then dried. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the title compound as colorless crystals(0.37 g, 70%). ^{1}H-NMR and IR spectra indicate that the product according to this Working Example is completely identical with that obtained in Working Example 3.

Working Example 5

Ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

A mixture of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (0.7 g) and trimethyltin azide (0.7 g) in toluene (15 ml) was heated under reflux for 4 days. The reaction mixture was concentrated to dryness and to the residue were added methanol (20 ml) and 1N-HCl (10 ml). The mixture was stirred at room temperature for 30 minutes and adjusted to pH 3 to 4 with 1N NaOH. After removal of the solvent, the residue was partitioned between chloroform and water. The organic layer was washed with water and dried, and the solvent was evaporated to dryness to give a syrup. The syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate - benzene afforded colorless crystals (0.35 g, 45%), m.p. 158-159°C.

Elemental Analysis for $C_{26}H_{24}N_6O_3$:			
	C(%)	H(%)	N(%)
Calcd.:	66.65;	5.16;	17.94
Found :	66.61;	5.05;	17.84

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.09(3H,t), 1.43(3H,t), 4.02(2H,q), 4.30(2H,q), 5.57(2H,s), 6.71(2H,d), 6.83-6.96(4H,m), 7.27-7.31(1H,m), 7.40(1H,dd), 7.55-7.66(2H,m), 8.04-8.09(1H,m)
IR(KBr) cm^{-1}: 1720, 1605, 1540, 1470, 1430, 1250, 1040, 750

Working Example 6

2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

A solution of ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.24 g) and 1N NaOH (1.5 ml) in ethanol (4 ml) was stirred at 80°C for one hour. The reaction mixture was concentrated, and the concentrate was extracted with water and ethyl acetate. The aqueous layer was adjusted to pH 3-4 with 1N-HCl to give crystals. Recrystallization of the crystals from ethyl acetate - methanol afforded colorless crystals (0.15 g, 67%), m.p. 183-185°C.

Elemental Analysis for $C_{24}H_{20}N_6O_3.1/5H_2O$:			
	C(%)	H(%)	N(%)
Calcd.:	64.91;	4.63;	18.93
Found :	65.04;	4.51;	18.77

^{1}H-NMR(200MHz,DMSO-d_6) δ : 1.38(3H,t), 4.58(2H,q), 5.63(2H,s), 6.97(4H,q), 7.17(1H,t), 7.47-7.68(6H,m)
IR(KBr) cm^{-1}: 1710, 1550, 1480, 1430, 1280, 1240, 1040, 760

Working Example 7

2-Ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (2.07 g) in methylene chloride (10 ml) were added trityl chloride (1.59 g) and triethylamine (0.8 ml). The mixture was stirred at room temperature for one hour. The reaction mixture was washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization of crude crystals thus obtained from ethyl acetate - benzene gave colorless crystals (2.12 g, 66%), m.p. 168-170°C.

Elemental Analysis for $C_{43}H_{34}N_6O_3$:			
	C(%)	H(%)	N(%)
Calcd.:	75.64;	5.02;	12.31
Found :	75.37;	4.96;	12.20

^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.40(3H,t), 4.61 (2H,q), 5.58(2H,s), 6.76(2H,d), 6.91-6.96(8H,m), 7.12(1H,t), 7.17-7.41 (12H,m), 7.60(1H,dd), 7.73-7.82(2H,m)

Working Example 8

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1 -[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate

To a solution of 2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (0.5 g) in DMF (5 ml) were added potassium carbonate (0.12 g) and cyclohexyl 1-iodoethyl carbonate (0.26 g). The mixture was stirred for one hour at room temperature. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was dissolved in methanol (10 ml) and to the solution was added 1N-HCl (2 ml). The mixture was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel to give colorless powder (0.21 g, 47%), m.p. 103-106°C.

Elemental Analysis for $C_{33}N_{34}N_6O_6$:			
	C(%)	H(%)	N(%)
Calcd:	64.91;	5.61;	13.76
Found :	64.94;	5.71;	13.66

To the powder (1 g) obtained as above was added ethanol (6 ml). The mixture was stirred for 3 hours at room temperature and allowed to stand under ice-cooling. The mixture was then stirred for one hour at temperatures not higher than 10°C. Resultant crystals were collected by filtration and washed with cold ethanol. The crystals were dried at 250C for 9 hours under reduced pressure, then at 35°C for further 18 hours to obtain white powdery crystals (0.94 g), m.p. 158-166°C (decomp.).

Elemental Analysis for $C_{33}H_{34}N_6O_6$:			
	C(%)	H(%)	N(%)
Calcd.:	64.91;	5.61;	13.76
Found :	64.73;	5.66;	13.64

^{1}H-NMR (200MHz) δ : 1.13-1.84(16H,m), 4.28-4.55(3H,m), 5.65(2H,d), 6.72(1H,q), 6.81(2H,d), 6.93(2H,d), 7.03(1H, t), 7.22-7.23(1H,m), 7.31-7.36(1H,m), 7.52-7.60(3H,m), 8.02-8.07(1H,m)
IR(KBr) cm^{-1}: 2942, 1754, 1717, 1549, 1476, 1431, 1076, 1034, 750 MS(m/z) : 611 $[M+H]^+$

Experimental Example 1

Stable C-type crystalline 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate and preparation thereof

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate is usually purified by column chromatography on silica gel and the eluted fraction is concentrated to dryness to give amorphous powders. The powder is unstable by heat and impractical in production. For solving this problem, the present inventors made extensive experiments on crystallization of the subject compound and discovered C-type crystalline form. The C-type crystal is unexpectedly stable by heat and quite useful for production. The C-type crystal

of the title compound has approximately the following lattice spacings:

3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle
5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak

IR spectrum (KBr tablet) of the C-type crystal is shown in Figure 2 with the significant absorption maxima at 2942, 1754, 1717, 1615, 1549, 1476 and 750 cm^{-1} and its melting point is 158-166°C (decomposition). Representative X ray chart (powder method), IR spectra (KBr tablet) and differential scanning calorimeter patterns are shown in Figures 1-3, respectively.

The C-type crystal of 1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate has advantages, for example;

1. It improves heat stability and practical utility.
2. Residual solvent can be minimized in crystals.
3. It can achieve industrial and clinical developments and give ecomomical benefits.

The concentrated residues, amorphous powders, and/or crystals except for the C-type crystal for obtaining the subject compound, are stirred in a suitable solvent to form the desired C-type crystal. In case where the C-type crystal is not formed, a small amount of the C-type crystal can be added as a seed to allow crystallization. Examples of such solvents are not limited to, as long as they afford the C-type crystal, but include lower alcohols (e.g. methanol, ethanol, isopropyl alcohol, etc.), a mixture of lower alcohol and water and a mixture of lower alkyl ketone (e.g. acetone, etc.) and water. Amounts of solvents used are not limited to, but practically, 2 to 30-fold per weight of the crystal. Ratios of lower alcohol vs. water and lower alkyl ketone vs. water are not limited to, but preferably 4:1 to 1:1. Stirring temperatures are not limited to, but -5°C to 40°C, preferably 0°C to 25°C.

Experimental Example 2

Inhibition of binding of angiotensin II to angiotensin receptor

[Method]

An experiment of inhibition on the binding of angiotensin II (A II) to A II receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685-696 (1978)]. An A II receptor membrane fraction was prepared from bovine adrenal cortex.

The compound of the present invention (10^{-6}M or 10^{-7}M) and ^{125}I-angiotensin II (^{125}I-A II) (1.85 kBq/50 µl) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-A II were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-A II bound to the receptor was measured.

[Results]

The results relating to the compounds of the present invention are shown in Table 2.

Experimental Example 3

Inhibitory effect of the compound of the present invention on pressor action of A II

[Method]

Jcl : SD rats (9 week old, male) were employed. On the previous day of the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed to access freely to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means of polygraph. Before administration of the drug, the pressor action due to intravenous administration of A II (100 ng/kg) as the control was measured. The drugs were orally administered, then, at each point of the measurement, AII was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on A II-induced pressor action was evaluated.

[Results]

The results relating to the compounds of the present invention are shown in Table 2.

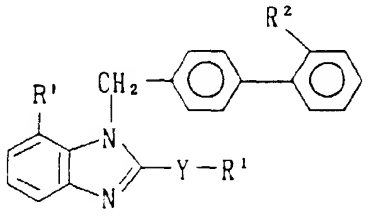


TABLE 2

Working Example No.	R¹	Y	R²	R'	Radioreceptor Assay 1x10 $^{-7}$M	1x10 $^{-6}$M	Pressor Response to A II (p.o.) 3mg/kg
5	Et	O	Tet	COOEt	46	82	+++ a)
6	Et	O	Tet	COOH	61	91	+++
8	Et	O	Tet	$COOCH(CH_3)OCO$-⬡	32	77	+++

Claims

1. 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid or a pharmaceutically acceptable salt thereof.

2. 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

3. A stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate.

4. A crystal according to claim 3, which has approximately the following lattice spacings according to X ray powder method:

3,5 angstrom; middle
3.7 angstrom; weak
3,8 angstrom; middle
4,0 angstrom; middle
4,1 angstrom; weak
4,3 angstrom; weak
4,4 angstrom; middle
4,6 angstrom; middle
4,8 angstrom; middle
5,1 angstrom; middle
5,2 angstrom; weak
6,9 angstrom; weak
7,6 angstrom; weak
8,8 angstrom; middle
9,0 angstrom; strong
15,9 angstrom, weak

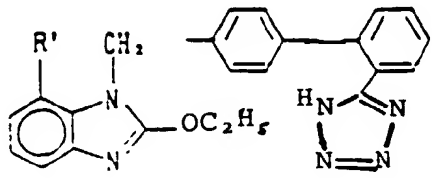
5. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a compound according to one of claims 1 or 2 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, excipient or diluent.

6. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a crystal according to claim 3 or 4 in admixture with a pharmaceutically acceptable carrier, excipient or diluent.

7. Use of a compound according to one of claims 1 or 2 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

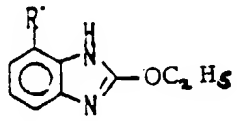
8. Use of a crystal according to claim 3 or 4 for the manufacture of a medicament for antagonizing angiotensin II.

9. A method for producing a compound of the formula (I):



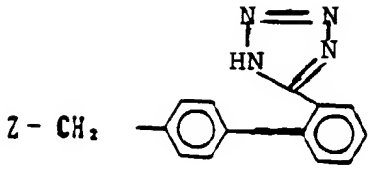
(I)

wherein R' is carboxyl or 1-(cyclohexyloxycarbonyloxy)-ethoxy carbonyl, or a pharmaceutically acceptable salt thereof, which comprises (i) reacting a compound of the formula (II):



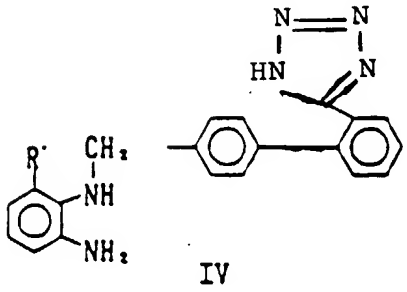
II

wherein R' has the above-defined meaning, or a salt thereof, with a compound of the formula (III):



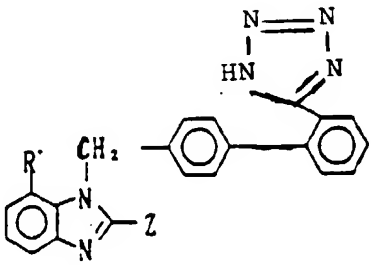
III

wherein Z is halogen, (ii) reacting a compound of the formula (IV):



IV

wherein R' has the above-defined meaning, or a salt thereof, with an alkyl orthocarbonate or a carbonylating reagent or (iii) reacting a compound of the formula (V'):



wherein each group has the above-defined meaning or a salt thereof, with a nucleophilic reagent, and, if desired, converting a product obtained by the above processes (i) to (iii) into a compound of the formula (I) by nucleophilic reaction, acylation, esterification, and/or deprotection, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition for treating circulatory diseases such as hypertensive diseases, which comprises a compound of one of claims 1 to 4 or a pharmaceutically acceptable salt thereof with a carrier, excipient or diluent.

Patentansprüche

1. 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazol-7-carbonsäure oder ein pharmazeutisch annehmbares Salz davon.

2. 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazol-7-carbonsäure-[1-(cyclohexyloxycarbonyloxy)ethyl]ester oder ein pharmazeutisch annehmbares Salz davon.

3. Stabiler Kristall von 2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazol-7-carbonsäure-[1-(cyclohexyloxycarbonyloxy)ethyl]ester.

4. Kristall nach Anspruch 3, der ungefähr die folgenden Gitterabstände gemäß der Röntgenpulvermethode hat:

3,5 Angström; mittel
3,7 Angström; schwach
3,8 Angström; mittel
4,0 Angström; mittel
4,1 Angström; schwach
4,3 Angström; schwach
4,4 Angström; mittel
4,6 Angström; mittel
4,8 Angström; mittel
5,1 Angström; mittel
5,2 Angström; schwach
6,9 Angström; schwach
7,6 Angström; schwach
8,8 Angström; mittel
9,0 Angström; stark
15,9 Angström; schwach.

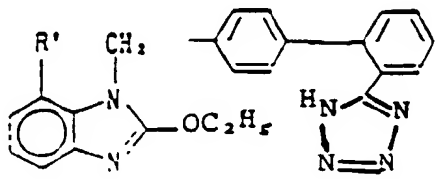
5. Pharmazeutische Zusammensetzung zum Antagonisieren von Angiotensin II, die eine therapeutisch wirksame Menge einer Verbindung gemäß einem der Ansprüche 1 oder 2 oder ein pharmazeutisch annehmbares Salz davon in Mischung mit einem pharmazeutisch annehmbaren Träger, Arzneimittelträger oder Verdünnungsmittel umfaßt.

6. Pharmazeutische Zusammensetzung zum Antagonisieren von Angiotensin II, die eine therapeutisch wirksame Menge eines Kristalls gemäß einem der Ansprüche 3 oder 4 in Mischung mit einem pharmazeutisch annehmbaren Träger, Arzneimittelträger oder Verdünnungsmittel umfaßt.

7. Verwendung einer Verbindung nach einem der Ansprüche 1 oder 2 oder eines pharmazeutisch annehmbaren Salzes davon für die Herstellung eines Medikaments zum Antagonisieren von Angiotensin II.

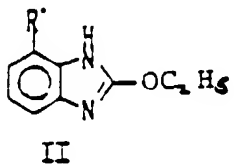
8. Verwendung eines Kristalls nach Anspruch 3 oder 4 für die Herstellung eines Medikaments zum Antagonisieren von Angiotensin II.

9. Verfahren zur Herstellung einer Verbindung der Formel (I):



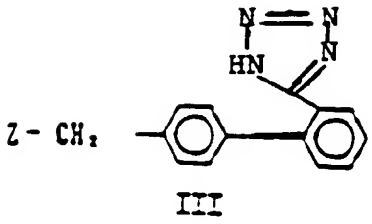
(I)

worin R' Carboxyl oder 1-(Cyclohexyloxycarbonyloxy)ethoxycarbonyl ist oder eines pharmazeutisch annehmbaren Salzes davon, das umfaßt (i) das Umsetzen einer Verbindung der Formel (II):



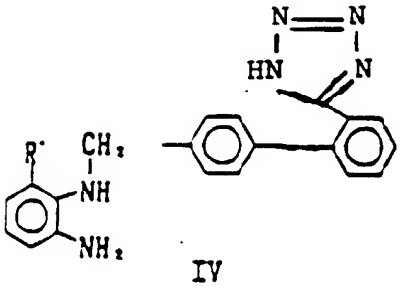
II

worin R' die oben definierte Bedeutung hat, oder eines Salzes davon, mit einer Verbindung der Formel (III):



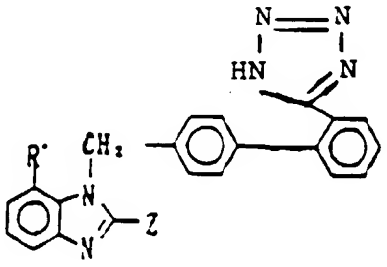
III

worin Z ein Halogen ist, (ii) das Umsetzen einer Verbindung der Formel (IV):



IV

worin R' die oben definierte Bedeutung hat, oder eines Salzes davon, mit einem Orthocarbonsäurealkylester oder einem carbonylierenden Reagenz oder (iii) das Umsetzen einer Verbindung der Formel (V') :



worin jede Gruppe die oben definierte Bedeutung hat, oder eines Salzes davon, mit einem nucleophilen Reagenz und, falls erwünscht, das Überführen eines durch die oben genannten Verfahren (i) bis (iii) erhaltenen Produkts in eine Verbindung der Formel (I) durch eine nucleophile Reaktion, Acylierung, Veresterung und/oder Entschützung und, falls gewünscht, die Überführung einer Verbindung der Formel (I) in ein pharmazeutisch annehmbares Salz davon.

10. Pharmazeutische Zusammensetzung zur Behandlung von Kreislauferkrankungen, wie beispielsweise Bluthochdruckerkrankungen, die eine Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch annehmbares Salz davon mit einem Träger, Arzneimittelträger oder Verdünnungsmittel umfaßt.

Revendications

1. Acide 2-éthoxy-1-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl}benzimidazole-7-carboxylique, ou l'un de ses sels admissibles en pharmacie.

2. 2-Ethoxy-1-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl}benzimidazole-7-carboxylate de 1-(cyclohexyloxycarbonyloxy)éthyle, ou l'un de ses sels admissibles en pharmacie.

3. Cristaux stables de 2-éthoxy-1-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl}-benzimidazole-7-carboxylate de 1-(cy-

clohexyloxycarbonyloxy)éthyle.

4. Cristaux conformes à la revendication 3, dont les distances interréticulaires ont à peu près les valeurs suivantes, d'après le diagramme de diffraction des rayons X par une poudre :

3,5 Å : intensité moyenne
3,7 Å : intensité faible
3,8 Å : intensité moyenne
4,0 Å : intensité moyenne
4,1 Å : intensité faible
4,3 Å : intensité faible
4,4 Å : intensité moyenne
4,6 Å : intensité moyenne
4,8 Å : intensité moyenne
5,1 Å : intensité moyenne
5,2 Å : intensité faible
6,9 Å : intensité faible
7,6 Å : intensité faible
8,8 Å : intensité moyenne
9,0 Å : intensité forte
15,9 Å : intensité faible

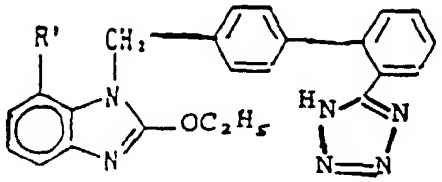
5. Composition pharmaceutique qui s'oppose aux effets de l'angiotensine II et qui contient, en une quantité thérapeutiquement efficace, un composé conforme à l'une des revendications 1 et 2 ou un sel admissible en pharmacie de l'un de ces composés, mélangé avec un véhicule, excipient ou diluant admissible en pharmacie.

6. Composition pharmaceutique qui s'oppose aux effets de l'angiotensine II et qui contient, en une quantité thérapeutiquement efficace, des cristaux conformes à la revendication 3 ou 4, mélangés avec un véhicule, excipient ou diluant admissible en pharmacie.

7. Emploi d'un composé conforme à l'une des revendications 1 et 2 ou d'un sel admissible en pharmacie de l'un de ces composés, pour préparer un médicament qui s'oppose aux effets de l'angiotensine II.

8. Emploi de cristaux conformes à la revendication 3 ou 4, pour préparer un médicament qui s'oppose aux effets de l'angiotensine II.

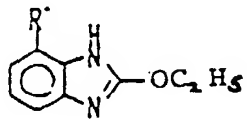
9. Procédé de préparation d'un composé de formule (I) :



(I)

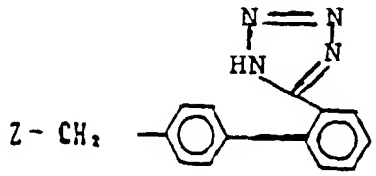
dans laquelle R' représente un groupe carboxyle ou 1-(cyclohexyloxycarbonyloxy)éthoxycarbonyle, ou d'un sel d'un tel composé, admissible en pharmacie, lequel procédé comporte :

1) le fait de faire réagir un composé de formule (II) :



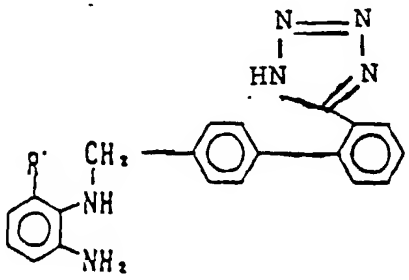
(II)

dans laquelle R' a la signification indiquée ci-dessus,
ou un sel de ce composé, avec un composé de formule (III) :



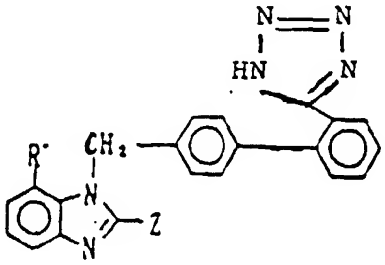
(III)

dans laquelle Z représente un atome d'halogène ;
2) le fait de faire réagir un composé de formule (IV) :



(IV)

dans laquelle R' a la signification indiquée ci-dessus,
ou un sel d'un tel composé, avec un orthocarbonate d'alkyle ou un réactif de carbonylation ;
ou bien
3) le fait de faire réagir un composé de formule (V) :



(V)

dans laquelle chaque symbole a la signification indiquée ci-dessus, ou un sel d'un tel composé, avec un réactif nucléophile ;
et si on le désire, le fait de transformer le produit obtenu selon l'un des procédés (1) à (3) ci-dessus en un composé de formule (I) par réaction nucléophile, acylation, estérification et/ou déprotection, et si on le désire, le fait de transformer un composé de formule (I) en l'un de ses sels admissibles en pharmacie.

10. Composition pharmaceutique destinée au traitement de maladies du système circulatoire, comme les maladies hypertensives, et contenant un composé conforme à l'une des revendications 1 à 4 ou un sel d'un tel composé, admissible en pharmacie, mélangé avec un véhicule, excipient ou diluant.

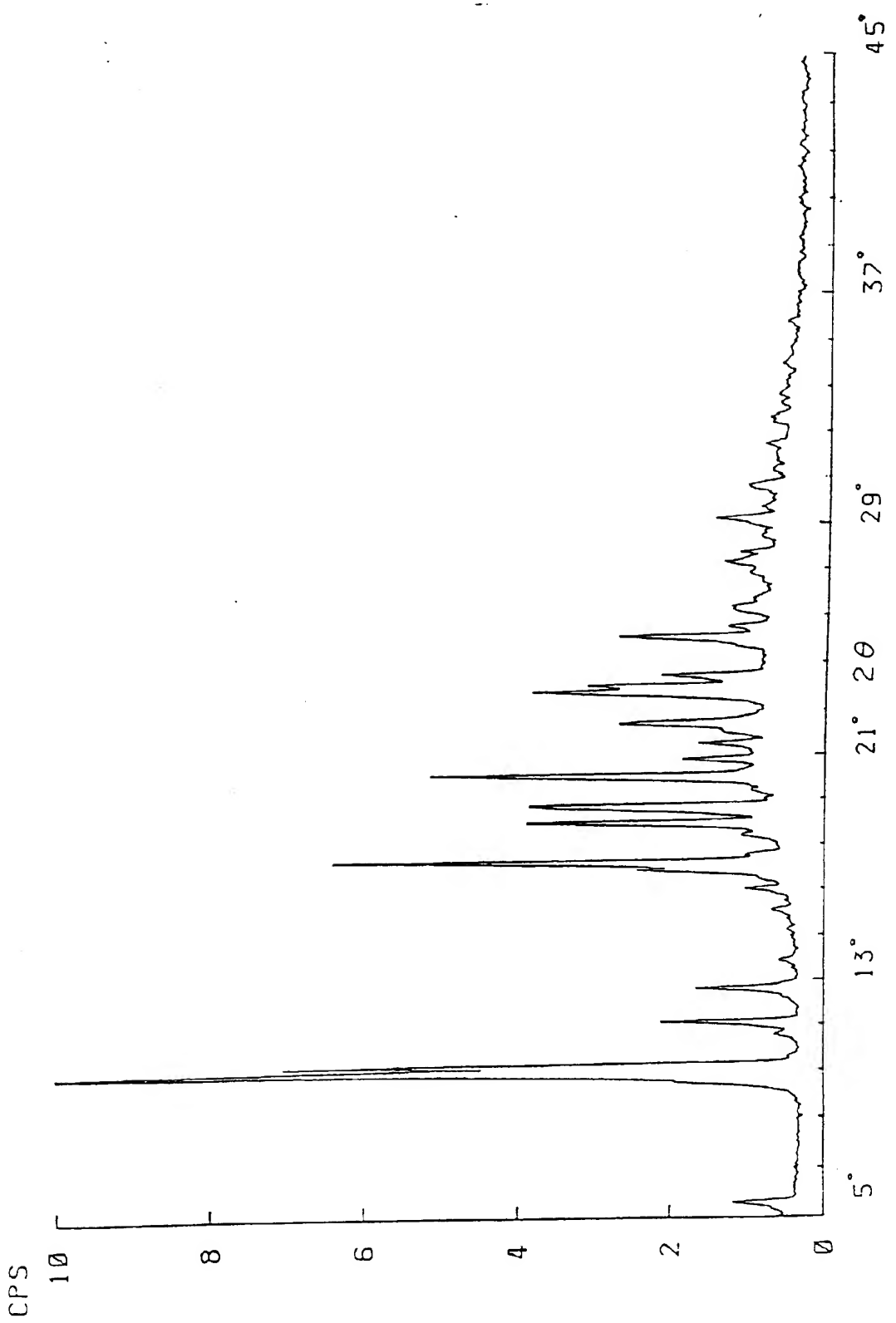


Figure 1

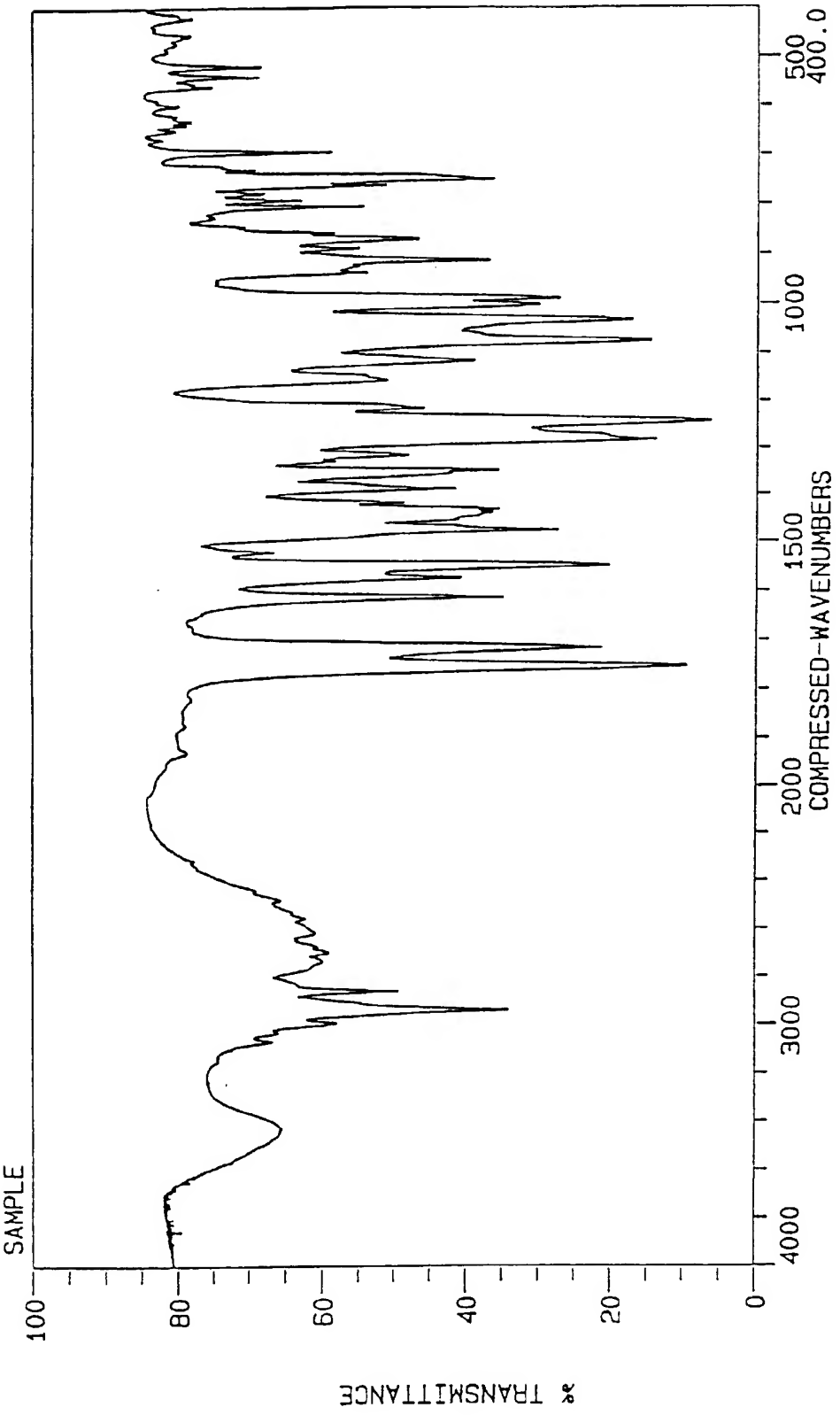

SAMPLE
100
80
60
40
20
0
% TRANSMITTANCE
4000
3000
2000
1500
1000
500
400.0
COMPRESSED-WAVENUMBERS

Figure 2

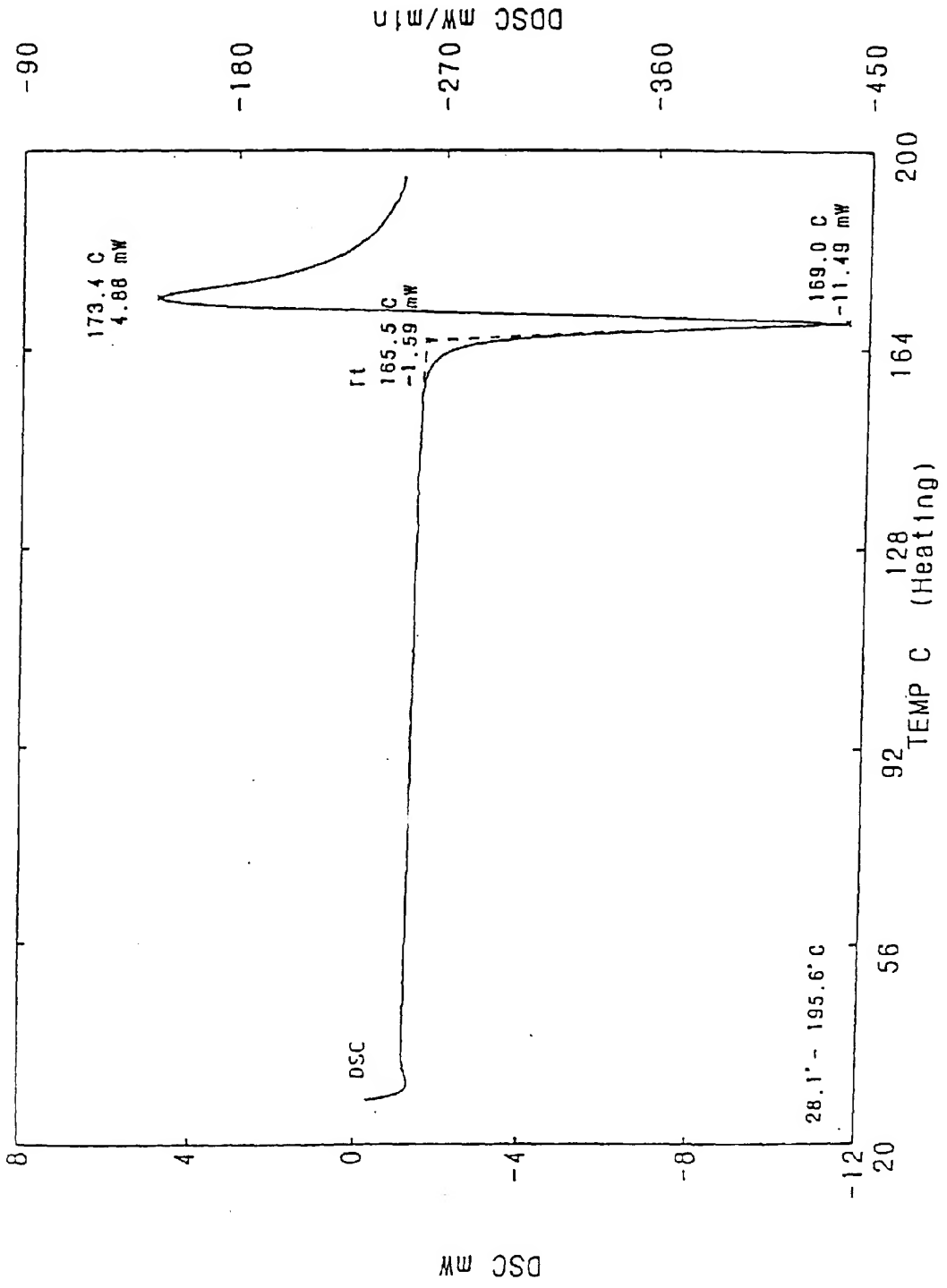

DSC mW/min
-90
-180
-270
-360
-450
173.4 C
4.88 mW
rt
165.5 C
-1.59 mW
169.0 C
-11.49 mW
DSC
28.1' - 195.6' C
8
4
0
-4
-8
-12
20
56
92
128
164
200
TEMP C (Heating)
DSC mW

Figure 3